REMARKS

The Pending Claims:

Claims 12-30 and 56-66 are pending in this application. Claims 12-30 and 56-66 are directed to a method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease. Claims 13-20 and 27-30 have been withdrawn from consideration by the Examiner as being drawn to a non-elected species. However, Examiner stated in the Office Action issued March 22, 2001 (Paper No. 5) that upon allowance of a generic claim (e.g., Claim 12), Applicant will be entitled to consideration of claims to additional species.

The Office Action and Applicant's Response

Examiner Navarro acknowledged that Applicant's amendment, received October 15, 2002 (Paper No. 17; mailed by Applicant on October 7, 2002) has been received and entered.

The Examiner confirmed that claims 12-30 and 56-66 are pending in the instant application, and he stated that Claims 12, 21-26, and 56-66 are under consideration.

In the pending Office Action, the Examiner stated that all grounds of rejection in the Office Action mailed June 6, 2002 are withdrawn.

The Examiner objected to Claims 24-25, and 57-66 as depending upon a rejected base claim, however the Examiner stated that Claims 24-25 and 57-66 are free of the prior art of record.

Accordingly, Applicant has added new Claims 67-79, directed to the claimed subject matter of Claims 24, 25, 26 (also dependent from Claim 24), and Claims 57-66, as originally filed, and supported by those originally filed claims.

Applicant has amended, merely for greater clarity, the final "whereby clause" of

Claim 12 to recite "whereby the *at least one* symptom is improved."

Further amendments to Claims 12 and 26 are described in detail hereinbelow.

In view of the amendment to Claim 12, Applicant has also made a merely refining amendment to Claim 27 to delete the recitation of "wherein the suspected diagnosis is of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease; and", which is superfluous in view of the deletion of "Crohn's disease from Claim 12.

The Examiner cited the following new grounds of rejection.

A. Rejections under 35 U.S.C. § 112, second paragraph

Claim 26 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of the phrase "derivative." The Examiner stated:

Since it is unclear how the bile acids are undergoing any kind of chemical modification as implied by the recitation of "derivative." Since it is unclear how the bile acids are to be derived as referred to in the claims, there is no way for the person of skill in the art to ascribe a discrete and identifiable definition to said phrase.

Applicant has overcome the ground of rejection by the amendment of Claim 26 deleting the phrase "or a derivative of either of these".

Therefore, the Examiner is respectfully requested to withdraw the rejection of Claim 26 on this ground.

B. Rejections under 35 U.S.C. § 102(b)

Claims 12 and 56 were rejected under 35 U.S.C. 102(b) as being anticipated by Rutgeerts *et al.* (Gastroenterology 76(5):1232 [1979]). The Examiner stated the following reasons:

... The claims are directed to a method of treating irritable bowel syndrome or Crohn's disease comprising detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom with a suspected diagnosis of irritable bowel syndrome or Crohn's disease, and at least partially eradicating the bacterial overgrowth, whereby the symptom(s) is improved.

Rutgeerts et al (Gastroenterology Vol. 76, No. 5, Part 2, p 1232,1979) disclose of detecting small intestinal bacterial overgrowth in patients with Crohn's disease. Rutgeerts et al further disclose of the administration of antibiotics to these patients.

In view that Rutgeerts et al disclose of detecting bacterial overgrowth in patients with Crohn's disease and subsequently administering antibiotics which will inherently partially eradicate the bacterial overgrowth, the disclosure of Rutgeerts et al is deemed to anticipate the claimed invention. It is further noted that patients with Crohn's disease exhibit rebound tenderness and thus are deemed to have the symptom of hyperalgesia.

A claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. *Verdgaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicant has overcome the rejection of Claim 12 and its dependent Claim 56 by amending Claim 12 to delete the phrase "or Crohn's disease" and to insert the phrase "an autoimmune disease *selected from the group consisting of multiple sclerosis and systemic lupus erythematosus*." The amendment is intended to clarify that Crohn's disease is excluded from among the conditions to which amended Claim 12 and 56 are directed. The amendment to Claim 12 is supported in the specification as originally filed, e.g., at page 19, lines 22-24; at page 20, lines 20-31; at page 35, line 11 through page 36, line 13 (in Example 5).

The cited Rutgeerts *et al.* reference fails to negate the novelty of amended Claim 12 (and Claim 56 dependent therefrom), which recites the step of "detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom associated with a suspected diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease selected from the group consisting of multiple sclerosis and systemic lupus erythematosus . . ." None of the teachings of Rutgeerts *et al.* relate to any of these conditions, but merely to Crohn's disease, which is not recited in amended Claim 12.

Therefore, the Examiner is respectfully requested to withdraw the rejection of Claims 12 and 56 on this ground.

C. Rejections under 35 U.S.C. § 103(a)

Claims 12, 21-23 and 56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rutgeerts *et al.* (Gastroenterology 76(5):1232 [1979]) in view of Wellmann *et al.* (Klin. Wochenschr. 60(7):371-74 [1982]) and Friedman (Gastroenterology Clinics of North America 20(2):313-24 [1991]). The Examiner stated the following reasons:

The claims are directed to a method of treating irritable bowel syndrome or Crohn's disease comprising detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom with a suspected diagnosis of irritable bowel syndrome or Crohn's disease, and at least partially eradicating the bacterial overgrowth, whereby the symptom(s) is improved; wherein an intestinal lavage or enema is used to partially eradicate the bacterial overgrowth or modifying the subjects diet.

The teachings of Rutgeerts et al are set forth above.

Rutgeerts et al do not teach of an intestinal lavage or enema to partially eradicate the bacterial overgrowth or modifying the subjects diet.

Wellmann et al (Kilin Wochenschr Vol. 60, No. 7, pp 371-374, 1982) teach of reduced hospitalization time for patients with Crohns disease who received intestinal lavages. (See abstract).

Friedman (Gastroenterology Clinics of North America Vol. 20, No. 2, pp 313-324, 1991) teach that elimination of beans, cabbage, lentils, brussel sprouts, and legumes from the diet may reduce the symptoms of irritable bowel syndrome. (See abstract).

Given that 1) Rutgeerts et al have taught of detecting small intestinal bacterial overgrowth in patients with Crohn's disease and further teach of the administration of antibiotics to these patients, and that 2) Wellmann et al have taught that intestinal lavages reduce the duration of Crohns disease, and that 3) Friedman have taught that the elimination of certain foods from the diet reduces the symptoms of Crohns disease, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have incorporated the intestinal lavages as taught by Wellmann et al or the altered diet as taught by Friedman with the method of treating Crohns disease as taught by Rutgeerts et al. One would have been motivated to combine the teachings based upon the demonstration of the reduction of symptoms of Crohn's disease as taught by both Wellmann et al and Friedman.

To establish a prima facie case of obviousness, each of three criteria must be met. (MPEP 2143). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination of references and the reasonable expectation of success must both be found in the prior art, and must not be based on hindsight provided by applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)(citing *In re Dow*

Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 [Fed. Cir. 1988]); *In re Dembiczak*, 175 F.3d 994, 998-1000 (Fed. Cir. 1999). Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. *In re Royka and Martin*, 490 F.2d 981, 180 USPQ 580, 583 (CCPA 1974). The examiner bears the burden of establishing a prima facie case of obviousness. *Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (B.P.A.I. 1993).

Applicant strongly disagrees that the cited references make obvious the invention claimed in Claims 12, 21-23, and 56, in view of the amendment to Claim 12. Applicant has amended Claim 12 and its dependent Claims 21-23, and 56 by amending Claim 12 to delete the phrase "or Crohn's disease" and to insert the phrase "an autoimmune disease *selected from the group consisting of multiple sclerosis and systemic lupus erythematosus*." The amendment is intended to clarify that Crohn's disease is excluded from among the conditions to which amended Claim 12 and 56 are directed. The amendment to Claim 12 is supported in the specification as originally filed, e.g., at page 19, lines 22-24; at page 20, lines 20-31; at page 35, line 11 through page 36, line 13 (in Example 5).

In view of the amendment to Claim 12 none of the cited Rutgeerts *et al.*, Wellman *et al.*, and Friedman references, separately or in combination, teaches or suggests the recited claim limitations of "*detecting the presence of small intestinal bacterial overgrowth* in a human subject having at least one symptom associated with *a suspected diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder*, or an autoimmune disease selected from the group consisting of *multiple sclerosis and systemic lupus erythematosus*," as recited in amended Claim 12.

Rutgeerts *et al.* failed to relate to any suspected diagnosis other than Crohn's disease, which is not recited in amended Claim 12.

Wellman *et al.* taught that intestinal lavage through a jejunal tube can reduce the

hospitalization time for Crohn's disease patients, and thus failed to relate to any suspected diagnosis other than Crohn's disease, which is not recited in amended Claim 12.

Friedman taught that the elimination of beans, cabbage, lentils, brussels sprouts, and legumes from the diet can reduce symptoms of postprandial bloating, flatus, and abdominal discomfort in irritable bowel syndrome (IBS), but Friedman related to effects caused by *colonic* flora (*i.e.,* fermentative bacteria in the colon; *e.g.*, Friedman, at page 319, last paragraph), not to effects of small intestinal bacterial overgrowth that is an abnormal phenemonon of the small intestine, which is normally free of bacterial contamination (see, specification, at page 15, lines 20-24). In relation to IBS, or to any of the other SIBO-associated conditions recited in amended Claim 12, Friedman failed to teach or suggest "*detecting the presence of small intestinal bacterial overgrowth* . . . and at least partially eradicating the bacterial overgrowth . . . ," minus the hindsight provided by Applicant's specification.

Consequently, there was no suggestion nor motivation, neither in any of the references themselves nor in the knowledge generally available to one skilled in the art, to combine Rutgeerts *et al.* and Wellman *et al.*, both of which related only to Crohn's disease, with Friedman, which failed to relate to small intestinal bacterial overgrowth, to obtain the claimed method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease selected from the group consisting of multiple sclerosis and systemic lupus erythematosus (e.g., Claim 12).

Therefore, in view of the amendment of Claim 12, the Examiner is respectfully requested to withdraw the rejection of Claims 12, 21-23 and 56 on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

By: _____
Nisan A. Steinberg, Ph.D.
Reg. No. 40,345

SIDLEY AUSTIN BROWN & WOOD
555 West Fifth Street, Suite 4000
Los Angeles, California 90013
Ofc: 213/ 896-6665
Fax: 213/ 896-6600

Version With Markings To Show Changes Made

In the Claims:

Please amend Claims 12, 26, and 27, and add new Claims 67-79 as follows.

12.(Amended) A method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease selected from the group consisting of multiple sclerosis and systemic lupus erythematosus,[or Crohn's disease,] comprising:

detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom associated with a suspected diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease selected from the group consisting of multiple sclerosis and systemic lupus erythematosus[, or Crohn's disease]; and at least partially eradicating the bacterial overgrowth, whereby the at least one symptom[(s)] is improved.

26.(Amended) The method of Claim 24, wherein the bile acid is ursodeoxycholic acid[,] or chenodeoxycholic acid[or a derivative of either of these], and the bile salt is a sodium or potassium salt of ursodeoxycholate or chenodeoxycholate[, or of a derivative of either of these].

27.(Twice Amended) The method of Claim 12, [wherein the suspected diagnosis is of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease; and]further comprising administering to said human subject an antagonist of a pro-inflammatory cytokine or an antibody that specifically binds an inflammatory cytokine, simultaneously

with or after at least partially eradicating small intestinal bacterial overgrowth in the human subject.

Please add new Claims 67-79

--67.(New) A method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease, comprising:

detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom associated with a suspected diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease; and

at least partially eradicating the bacterial overgrowth by administering to the human subject a chemical prokinetic agent selected from the group consisting of a peptide, a macrolide compound, a bile acid, a bile salt, a cholinergic compound, a dopamine antagonist, a nitric oxide altering agent, a 5-HT receptor antagonist, a neuroleptic agent, a kappa agonist, or an antihistamine except ranitidine, famotidine, or nizatidine, whereby phase III interdigestive intestinal motility in the human subject is increased and the bacterial overgrowth is thereby at least partially eradicated, and whereby the at least one symptom is improved.

68.(New) The method of Claim 67, wherein the prokinetic agent is cisapride, metoclopramide, domperidone, bethanechol, erythromycin, azithromycin, nomega-nitro-L-arginine methylester, or N-monomethyl-L-arginine, ondansetron, alosetron, promethazine, meclizine, prochlorperazine, chlorpromazine, haloperidol, or fedotozine.

69.(New) The method of Claim 67, wherein the bile acid is ursodeoxycholic acid or chenodeoxycholic acid, and the bile salt is a sodium or potassium salt of ursodeoxycholate or chenodeoxycholate.

70.(New) A method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease, comprising:

detecting the presence of small intestinal bacterial overgrowth (SIBO) in a human subject having hyperalgesia associated with a suspected diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease; and

alleviating or improving the hyperalgesia by administering an agent that modifies afferent neural feedback or sensory perception, whereby the hyperalgesia is improved.

71.(New) The method of Claim 70, wherein the agent that modifies afferent neural feedback or sensory perception is a 5-HT receptor antagonist, an opiate agonist, peppermint oil, cisapride, a dopamine antagonist, an antidepressant agent, an anxiolytic agent, or a combination of any of these.

72.(New) The method of Claim 71, wherein the dopamine antagonist is domperidone.

73.(New) The method of Claim 71, wherein the opiate agonist is fedotozine.

74.(New) The method of Claim 71, wherein the 5-HT receptor antagonist is ondansetron or alosetron.

75.(New) The method of Claim 71, wherein the antidepressant agent is a tricyclic antidepressant, tetracyclic antidepressant, a serotonin re-uptake inhibitor, a monoamine oxidase inhibitor, trazodone, venlafaxine, mirtazapine, nefazodone, or bupropion.

76.(New) The method of Claim 75, wherein the tricyclic antidepressant is amitriptyline and the tetracylic antidepressant is maprotiline.

77.(New) The method of Claim 75, wherein the monoamine oxidase inhibitor is phenelzine.

78.(New) The method of Claim 75, wherein the serotonin re-uptake inhibitor is fluoxetine or sertraline.

79.(New) The method of Claim 71, wherein the anxiolytic agent is a benzodiazepine compound.--.